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Atty Dkt. No.: STAN147
USSN: 09/628,494

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Typed or Printed Name: Steven F. Goldstein		
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RESPONSE TO RESTRICTION REQUIREMENT and SUPPLEMENTAL PRELIMINARY AMENDMENT	Application No.	09/628,494
	Confirmation No.	N/A
	Filing Date	July 28, 2000
	First Named Inventor	Emmanuel Mignot
	Examiner	J. Souaya
Address to: Commissioner of Patents and Trademarks Washington, D.C. 20231	Group Art Unit	1655
	Docket No.	STAN147

Sir:

This communication is in response to the Restriction Requirement dated September 21, 2001, which set a one month period for reply to make a response due on or before October 21, 2001. This response is filed with a Petition for a One-Month Extension of Time to extend the due date to and including November 21, 2001. Therefore, this response is timely filed.

Prior to examination of the application on the merits, please amend the claims as follows:

AMENDMENTS

In the Claims:

Cancel claims 4 and 13-37 without prejudice to renewal.

No claims are amended.

Please replace the claims with their correspondingly numbered pending claims provided below so as to provide a complete record of the claims pending after entry of this amendment.

1. A method for detecting a predisposition to a disorder in a subject caused by an alteration in hypocretin receptor activity, the method comprising:

analyzing nucleic acid of a subject for the presence of at least one polymorphism that predisposes the subject to a disorder caused by an alteration in activity of a hypocretin receptor;

wherein the presence of the predisposing polymorphism is indicative of an increased susceptibility of the subject to a disorder caused by an alteration in a hypocretin receptor activity.

2. The method of claim 1, wherein the predisposing polymorphism is in a hypocretin receptor gene.

3. The method of claim 1, wherein the predisposing polymorphism is in a hypocretin receptor-2 gene.

5. The method of claim 1, wherein the disorder is a sleep disorder.

6. The method of claim 5, wherein the predisposing polymorphism causes a sleep disorder characterized by decreased wakefulness.

7. The method of claim 5, wherein the predisposing polymorphism causes a sleep disorder characterized by increased wakefulness or insomnia.

8. The method of claim 5, wherein the disorder is narcolepsy.

9. The method of claim 1, wherein the disorder is selected from the group consisting of a mood disorder, chronic fatigue syndrome and an attention deficit disorder.

10. The method of claim 1, wherein the subject is human.

11. The method of claim 1, wherein the subject is canine.

12. The method of claim 11, wherein the polymorphism to be detected is within a genomic region between markers 26-8 and 530-3, inclusive, of canine chromosome 12.

38. An isolated nucleic acid molecule comprising at least 15 contiguous nucleotides and capable of hybridizing under high stringency conditions to a sequence encoding a mutated canine hypocretin receptor or a complement of said sequence encoding a mutated canine hypocretin receptor, which mutated hypocretin receptor causes canine narcolepsy.

39. The isolated nucleic acid molecule of claim 38, wherein the probe hybridizes specifically to a sequence encoding an amino acid having a sequence of SEQ ID NO:10.

40. The isolated nucleic acid molecule of claim 38, wherein the probe hybridizes specifically to a sequence encoding an amino acid having a sequence of SEQ ID NO:11.

41. The isolated nucleic acid molecule of claim 38 further characterized by specific hybridization to SEQ ID NO:13.

42. The isolated molecule of claim 38 further characterized by specific hybridization to SEQ ID NO:15.

43. A kit comprising the isolated nucleic acid molecule of claim 38, wherein the kit is useful in detecting a narcolepsy susceptibility locus in a canine subject.

44. A kit for use in detection of a canine narcolepsy susceptibility locus, the kit comprising at least one primer for amplification of a narcolepsy informative region, wherein the primer is selected from the group consisting of SEQ ID NOS:32-53.

45. The method of claim 11, wherein the polymorphism is a truncated HCRtr2 transcript.

REMARKS

Claims 1-3, 5-12 and 38-45 are pending after entry of the amendment herein.

Claims 4 and 13-37 are canceled without prejudice as being directed to a non-elected invention.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Interview Summary

Applicants are grateful for the telephonic interview with the undersigned on November 15, 2001. After discussing the restriction requirement during the teleconference, it was agreed that the restriction requirement would be recast in the first Office Action on the merits in order to divide the method claims and the composition claims of Group I into separate groups. Nevertheless, the Examiner requested that applicants make a election based upon the present restriction requirement, which election is provided below.

Restriction Requirement

The Office Action set out several requirements, which are outlined below.

Restriction requirement

The Examiner therein required election of one of the following groups of claims:

Group I: Claims 1-3, 5-12 and 38-45, drawn to a method for detecting a predisposition to a disorder in a subject caused by an alteration in hypocretin receptor activity using nucleic acid based assays, and to nucleic acids for detecting polymorphisms in hypocretin receptor;

Group II: Claims 4 and 32-37, drawn to detecting a predisposition to a disorder or to methods of detecting a sleep disorder or a predisposition to a sleep disorder using protein based assays;

Group III: Claims 13-26, drawn to a method for screening biologically active agents that modulate sleep through modulation of hypocretin receptor activity, and to methods of treatment; and

Group IV: Claims 27-31, drawn to methods for detecting a predisposition to a sleep disorder by detecting an autoimmune response.

Election of a nucleic acid that detects a single polymorphism

In addition, the Office Action indicated that if Group I is elected, applicants must further elect a nucleic acid that detects a single polymorphism (refers to claims 39-42 and 45) on the grounds that these nucleic acids are drawn to nucleic acids the encode different proteins. The Office Action stressed that this is not an election of species requirement.

Primers of claim 44 that detect the elected polymorphism

The Office Action also further required that, upon election of Group I, that applicants indicate which primers in claim 44 are directed to the polymorphism elected as a search of all 22 primers represents a serious burden to the Examiner, and as such are subject to further restriction if the primers are drawn to different nucleic acids encoding different proteins.

Relationship of SEQ ID NOS:13, 15, 10, and 11, and the polymorphism of claim 45

The Office Action further asserts that the specification does not set for the relationship between the nucleic acids of SEQ ID NOS:13 and 15, and the nucleic acids encoding the amino acids of SEQ ID NOS:10 and 11, or the polymorphism of claim 45. Thus, the Office Action concludes, absent evidence to the contrary, these sequences and polymorphisms appear to be directed to nucleotide sequence encoding different proteins, and as such are subject to further restriction.

Overview of the Invention

Before responding, applicants would like to take this opportunity to provide an overview of the claimed invention, particularly as it is defined by the claims of Group I. The inventors have shown in both narcoleptic dogs and in humans that a defect in the hypocretin system is

associated with sleep disorder. If this system is disrupted (*e.g.*, due to, for example, a defect in the hypocretin receptor, or a defect in the hypocretin ligand), then the subject is likely to suffer from a sleep disorder such as narcolepsy. All primers to be used are designed to detect this phenomenon.

In dogs, which are an animal model for sleep disorders in humans, the inventors showed that an exemplary polymorphism of interest is an alteration in the hypocretin receptor 2 (Hcrtr2) sequence that affects production of a full-length functional polypeptide. See, *e.g.*, page 22, line 16 to page 26, line 9, and Examples 1-2 (page 42, line 23 to page 56, line 11).

In humans, the inventors showed that an exemplary polymorphism of interest is an alteration in the hypocretin ligand sequence. See, *e.g.*, page 27, line 1 to page 28, line 4, and Examples 5-6 (page 60, line 4 to page 68, line 12).

We note that the term "polymorphism", while encompassing single nucleotide polymorphisms (SNPs), are not limited to such. Polymorphisms associated with sleep disorder as encompassed within the claims of Group I can include any alteration in a nucleic acid sequence that leads to production of a hypocretin ligand or hypocretin receptor that does not function properly. Examples include alterations in the genomic sequence (*e.g.*, within the non-coding region) that lead to alternative splicing and production of a hypocretin receptor that is truncated relative to wild-type, alternations that affect the coding sequence so as to affect interaction of the hypocretin ligand with its receptor, and the like.

Election and Traversal of Restriction Requirement

Each aspect of the Restriction Requirement outlined above is addressed below.

Election

Applicants hereby elect to prosecute the claims of Group I, claims 1-3, 5-12 and 38-45, with traverse. The grounds for traversal are provided below. Applicants expressly reserve the right under 35 USC §121 to file a divisional application directed to the non-elected subject matter or any subject matter disclosed in this application during the pendency of this application.

Election of a nucleic acid that detects a single polymorphism

In addition, the Office Action indicated that if Group I is elected, applicants must further elect a nucleic acid that detects a single polymorphism (refers to claims 39-42 and 45) on the grounds that these nucleic acids are drawn to nucleic acids the encode different proteins. The Office Action stressed that this is not an election of species requirement.

Applicants respectfully traverse this requirement. However, in order to ensure that the present response is complete, applicants elect, with traverse, the hypocretin receptor polymorphism associated with the SINE insertion as illustrated in Fig. 6.

Traversal is based on the grounds that a requirement that applicants elect a single nucleic acid sequence for prosecution of both the method and the composition claims within Group I. While applicants do not agree with the requirement of election of a single nucleic acid with respect to the compositions claims, traversal of the election requirement is focused upon this requirement as it may be applied to the method claims.

The patentability of the method claims is not dependent upon the detection of a novel nucleic acid sequence or the use of novel primers or probes to detect such nucleic acid sequences. It is well-settled that claims that encompass a new use of an old compound are patentable.[1] Thus, the requirement for election of a single nucleic acid sequence polymorphism due to the burden of a search to determine the novelty of the sequences does not reasonable. Applicants are entitled to prosecution of method claims that encompass detection of all hypocretin receptor and hypocretin ligand polymorphisms without regard to whether the sequences detected or the sequences used in detection are novel. The invention lies not in the discovery of a new sequence, but rather in the recognition that disruption of the hypocretin system is associated with sleep disorders, and thus detection of such alterations is indicative of the susceptibility of the subject to a sleep disorder.

Applicants respectfully request that the requirement for election of species, particularly with respect to the method claims of Group I, be withdrawn.

Primers of claim 44 that detect the elected polymorphism

The Office Action also further required that, upon election of Group I, that applicants indicate which primers in claim 44 are directed to the polymorphism elected as a search of all 22 primers represents a serious burden to the Examiner, and as such are subject to further restriction if the primers are drawn to different nucleic acids encoding different proteins.

Applicants respectfully traverse this provisional requirement and the indication that the primers may be subject to further restriction, essentially for the same reasons discussed above in the context of the method claims. The methods of the invention should not be limited to the use of novel compositions -- or to the detection of novel sequences -- since method claims can be patentable even where old compositions are used. Furthermore, the methods of the invention do not require detection of alterations in coding sequences, as alterations in genomic, non-coding sequences of hypocretin ligands and hypocretin receptors can result in production of proteins that do not function as wild-type and thus are associated with susceptibility of the subject to sleep disorder. For example, alterations in a non-coding region that affects splicing can result in production of a truncated protein product which does not function as wild-type.

[1] See, *e.g.*, MPEP § 2112.02.

In order to ensure that applicants are fully responsive, applicants note that the primers of claim 44 are exemplary primer pairs designed for the amplification of regions of the canine hypocretin receptor, Hcrtr2.

Relationship of SEQ ID NOS:13, 15, 10, and 11, and the polymorphism of claim 45

The Office Action further asserts that the specification does not set for the relationship between the nucleic acids of SEQ ID NOS:13 and 15, and the nucleic acids encoding the amino acids of SEQ ID NOS:10 and 11, or the polymorphism of claim 45. Thus, the Office Action concludes, absent evidence to the contrary, these sequences and polymorphisms appear to be directed to nucleotide sequence encoding different proteins, and as such are subject to further restriction.

Again, applicants traverse any requirement that applicants elect a single nucleotide sequence, essentially for the reasons stated above with respect to the method claims of Group I. However, as a point of clarity, applicants note that the relationship of SEQ ID NOS:13 and 15 are illustrated in Fig. 6, and contain the sequences of a canine SINE element in a narcoleptic dog (SEQ ID NO:13), and a sequence at a 5' splice site in a narcoleptic dog (SEQ ID NO:15). SEQ ID NO:11 (also shown in Fig. 5) provides the amino acid sequence of a truncated canine hypocretin receptor that is produced depending upon the presence or absence of the SINE element of SEQ ID NO:13. SEQ ID NO:10 (also shown in Fig. 5) provides the amino acid sequence of a truncated canine hypocretin receptor that is produced depending upon the presence or absence of the single nucleotide polymorphism in the 5' splice site illustrated by SEQ ID NO:15. In short, the canine hypocretin receptor amino acid sequences are the products of the polymorphisms illustrated in Fig. 6.

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The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN147.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: November 20, 2001

By: _____
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